REMARKS

1. Election/Restriction

The species restriction has been withdrawn but the group level restriction between prostate cancer and NSCLC has been maintained.

2. Prior Art

2.1. All claims are rejected as obvious. In the principal rejection, the examiner contends that Palmer (2001) teaches selecting of individuals with stage IIIB or IV, priming them with cyclophosphamide, and then administering a liposome comprising BLP25 and lipid A. The examiner concedes that Palmer does not teach selecting patients having "stage IIIB locoregional (without malignant pleural effusion) NSCLC". However, the examiner says that Sugiura (1999) teaches that distinguishing between stage IIIB with pleural effusion and stage IIIB without pleural effusion is necessary for treatment selection because patients with pleural effusion cannot be treated with combined chemotherapy/immunotherapy, and also that the presence or absence of pleural effusion affects prognosis. Thus, according to the Examiner, it is prima facie obvious to modify Palmer's method to select the IIIB patients without pleural effusion.

In table 1, of Palmer (2001), eight patients (3 with IIIB, 5 with IV) were given a 20μg dose of BLP25. An additional 9 patients (3 with IIIB, 6 with IV) were given a 200 μg dose of BLP25. However, survival was monitored for only 8 of these patients. One 200 μg patient apparently had "clinical progression" prior to treatment, and hence was excluded from the treatment analysis. See sentence bridging cols. 1-2 of page 52. We note that it was one of the 200 μg patients because it has n=9 in Table 1 but n=8 in Fig. 3. Thus, for survival analysis purposes, there were either 2 with IIIB and 6 with IV in the 200 μg group, or 3 IIIB's and 5 IV's. The reader would not know which.

For the 20 μg dose group, the median survival was 5.4 months, and for the 200 μg dose group[1], it was 14.6 months (Fig. 3). There is no breakdown, of median survival between stage IIIB and stage IV, let alone between IIIB with and IIIB without pleural effusion.

A person of ordinary skill in the art would appreciate that this was a mere "phase I safety and dose comparison study", designed to determine the "safety profile" of the BLP25 liposomal vaccine and "its ability to generate an anti-MUC1 immune response." (page 50, top of column 2). Note that eliciting an immune response doesn't imply that the drug provides a clinically meaningful improvement in survival.

The Palmer study had no controls. Figure 3 attempts to use the 20 ug group as a control for the 200 ug group. A person of ordinary skill in the art would be likely to heavily discount any report of a difference in median survival rates between two groups of a mere eight patients each. The stated P value for the observed difference (14.6 months vs. 5.4 months) was 0.4844, i.e., there is over a 48% probability that the observed difference could arise by chance even if the sample was drawn from a population satisfying the null hypothesis.

Now, that P value was calculated for a comparison of overall survival in patient groups containing both stage IIIB and stage IV patients. If the comparison were limited to just the at most three stage IIIB patients, the median survivals would have been different and the P value most likely, given the group size, would have been even higher.

Palmer does not report the breakdown of the stage IIIB patients between those with locoregional disease and those with malignant pleural effusion. The implication is that the Palmer group did not believe that the distinction was a clinically relevant one.

So far as the person of ordinary skill in the art would

---

[1]

know, all of Palmer's two or three surival-monitored IIIB patients might have had IIIB with malignant pleural effusion. In such case, then it would be unknown whether the vaccine had the same, more or less value in treating patient with IIIB locoregional.

In this regard, note that in the later phase II study (Butts 2005, copy enclosed), it was expected that only 10% of the enrolled patients would have stage IIIB LR and 90% would have IIIB-MPE or IV. (page 6676, under "Statistical Analysis").

***

In 1997, Sugiura identified pleural effusion as a "significant prognostic factor". According to Sugiura, the median survival rates are as follows:

IIIB without effusion 15.3 months,
IIIB with effusion 7.5 months,
IV 5.5 months[2],

but the difference between IIIB with effusion and IV was not statistically significant. Survival curves are given in Sugiura Fig. 1 and looking there, we estimate two-year survival as being
~17% IIIB with pleural effusion;
~43% IIIB without;
~7% IV.

The overall IIIB/IV survival was median 6.5 months, and 11% at two years.

As noted by Sugiura, patients with IIIB locoregional

---

[2] Implying monthly survival rates of log (5)/log (15.3).

disease can be treated with combined chemotherapy and radiotherapy, whereas those with IIIB with malignant pleural effusion cannot (page 50, col. 1). Hence, even if Palmer's data were sufficient to persuade the art that BLP25 liposomal vaccine was efficaceous against NSCLC, Sugiura would motivate the skilled worker to use it to treat the conditions not susceptible to chemoradiotherapy, i.e, IIIB-MPE and IV.

The fact that Sugiura finds that the survival rate is different (and more like stage IV) in pleural effusion stage III patients than in non pleural effusion patients and that he concludes that pleural effusion is an independent indicator in prognosis, does not necessarily mean that they would behave differently than non pleural effusion stage III patients when treated with immunotherapy.

The examiner argues that the longer survival time of the IIB-locoregional group allows for a longer time to develop an immune response. The immunization schedule used in Palmer was spread over a 9 week period (immunizations at weeks 0, 2, 5 and 9). That is, of course, a substantial fraction of the median survival time for stage IV patients.

Nonetheless, if Palmer is evidence of a protective effect at all, it is on stage IV patients. From the Kaplan-Meier survival curve, it can be seen that the eight patients in the 200 group had the following survivals (estimated from the figure): 3, 4, 8, 14, 15, 16, 18.5 and 27. This is consistent (given the inaccuracies inherent in converting graphical representation back to numeric data) with the stated overall median survival of 14.6, 14.5 being the average of the fourth and fifth values set forth above.

If we assume that there were two IIIB patients in the survival analysis, and that they were the two longest survivors, we would be left with a median stage IV survival of 11 (average of 8 and 14), which is twice the 5.5 reported by Sugiura.

If there were three IIIB patients, and they were the three longest survivors, the median stage IV survival would be 8. However, it doesn't seem very likely that if there were three IIIB patients, that they were all IIIB-LR, and according to Sugiura, the IIIB-MPE survival times weren't statistically different from the IV survival times.

Since the putative effect was manifested after a nine week immunization, there is insufficient reason to infer that the longer "grace period" offered by Sugiura's stage IIIB LR patients would be needed in order to achieve an increase in survival.

Indeed, no such inference was made by the present inventors. The analysis of IIIB-LR survival was "posthoc", see Butts (2005) at 6679 col. 2. Indeed, even in 2007, there are still skeptics; see Sangha (2007), "Open Discussion", comments of Dr. Bruce Johnson.

We also respectfully assert that the present specification evidences an unexpectedly superior result, i.e., we helped patients with IIIB locoregional more than could be expected given their normal survival rates, given the improvement that would reasonably be expected from Palmer to be attributable to BLP25 treatment.

The survival study reported in the patent application (See pp. 35-27 and Figures 1 and 2) is summarized in the table below:

	BSC	Vaccine	Total	BSC	Vaccine
IIIB-LR	30	35	65	2y: 36.7%	2y: 60%
				med: 13.3m	med: *
	Hazard Ratio 0.5237 with 95% CI of 0.2607-1.0521 Adjusted Cox p=0.0692				

IIIB-MPE or IV	53	53	106	not stated	not stated
Overall	83	88	171	2y: 28.9%	2y: 42%
				med: 13.0m	med: 17.4m
	Hazard Ratio 0.7390 with 95% CI of 0.5089-1.0731 Adjusted Cox p=0.1120				

* The median survival for the vaccine arm could not be calculated because patient survival, still had not dropped to 50%. (Figure 2). **The minimum median survival was 24 months, see P37, L3.**

It can be seen from Figure 2 that the difference in survival curves led, using an adjusted Cox proportional hazards model, to a calculated hazard ratio for the vaccine-treated IIIB-LR group of 0.5237, i.e., a relative reduction in the death rate of almost 48%. It is true that the p value is 0.0692, which would be considered marginally statistically significant,[3] but the p value does not tell the whole story. One must look at the magnitude of the hazard ratio, which is quite impressive, and also at the positioning of the confidence band. It extends only slightly above 1, but down as low as 0.2607 (i.e., risk reduction of 74%). These are extremely promising results.

Moreover, the difference in two year survival rates is also quite promising. Since Palmer does not address two year survival rates, Palmer can hardly be said to render obvious the observed improvement in two year survival rates.

On page 38, Applicants also provide a quality of life comparison. There were statistically significant differences

[3] If a one-tailed test were used on the basis that Palmer (2001) had already demonstrated that the vaccine was not harmful, the p value would have been halved, to 0.0346, which is statistical significant by the traditional 0.05 criterion.

in the FACT-L total scores for the vaccine and control arms of the IIIB-LR subpopulation at both 19 weeks from baseline (p=0.027) and 31 weeks from baseline (p=0.008). Palmer and Sugiura do not address quality of life changes and therefore cannot be said to render amended claim 18 or new claim 40 obvious.

Extended (post-filing) survival data is provided by Sangha and Butts, "L-BLP25: A Peptide Vaccine Strategy in Non-Small Cell Lung Cancer," Clin. Cancer Res. 13 (15 Suppl) 4652s-4654s (August 1, 2007) and Butts, et al., "Randomized Phase IIB Trial of BLP25 Liposome Vaccine in Stage IIIB and IV Non-Small Cell Lung Cancer," J. Clin. Oncol. 23: 6674-81 (September 20, 2005)(copies enclosed).

The 2005 paper provides updated hazard ratio calculations for both the overall population (0.7300) and the (IIIB-MPE + IV) subpopulation (0.9069). The median survival for the vaccine arm of the IIIB-LR subpopulation was still unknown since over 54% were alive (page 6680, top col. 1). However, since the present claims are limited to treatment of IIIB-LR patients we are more interested in the 2007 paper. This reports, finally, a median survival for the vaccine arm of 30.6 months (versus the previously reported 13.3 for the control arm), with a hazard ratio of 0.55 at an adjusted Cox p value of 0.16.

There is further information in Kallen, "Market & Patients Access to New Oncology Products in Europe (Brussels, November 29, 2007) http://www.bdaoncology.org/docs/20071129Kallen.pdf ; this stated (page 11, copy enclosed) the hazard ratio as being 0.548, with a 95% CI of 0.301-0.999. It also provided the one-, two- and three-year survival rates:

	BSC	Vaccine
1 year	57%	69%

2 year	33%	57%
3 year	27%	49%

The post-filing results confirm that the drug may be of substantial clinical importance even though the power of the test (a function of the size of the IIIB-LR subpopulation) was not sufficient to prove the traditional statistical significance of the hazard ratio. (The phase II study in question was powered to detect a five month **overall** survival difference with a power of 80%, see page 4653s, col. 2.)

The dramatic result in stage IIIB-LR was entirely unexpected in the light of the Palmer 2001 data. That study showed around 9 months survival benefit, while our phase 2b trial, which is what the patent application is based on, showed a 17.3 months survival benefit in the stage III-LR population.

In the Palmer trial, all treated patients were dead by 27 months, while many patients in the phase 2b trial are still alive more than 6 years after starting treatment (news release attached). See e.g. http://www.drugs.com/clinical_trials/oncothyreon-announces-presentation-long-term-stimuvax-data-world-conference-lung-cancer-7863.html

Using our Fig. 1 overall survival data as a surrogate for Palmer's overall survival data, the vaccine increased median survival from 13 months to 17.4 months, which is an absolute change of 4.4 months, but about a one-third improvement. Our Fig. 2, relating to just the IIIB-LR subpopulation, shows an improvement in median survival from 13.3 (control) to a minimum of 24 months, thus an increase of 10.7 months, or nearly 100%. If we use the 30.7 median survival resulting from the follow-up reported by Kallen, the improvement is 17.4 months, or about 130%.

Sugiura, as previously noted, observed a 15.3 month

median survival in IIIB locoregional. Hence, one relying on Fig. 1 as evidence of the quantitative effect of BLP25 arguably would expect it to provide a one third improvement, i.e., to a bit over 20 months. Whereas its improvement as shown by the 2007 median survival followup was to almost 31 months. This is an unexpected superiority.

2.2. Claim 22 (with a MUC-1 peptide dosage of 100 μg) is rejected over Palmer (2001) and Sugiura, in further view of Palmer, Abstract 179 PD (2000) ("Palmer2").

This abstract provides only very limited information on treatment results. There were eight patients with IIIB or IV, no info given on how many with each. Each patient was given 1000μg BLP25 weekly. This was a follow-up to the phase I trial, with 200 μg doses, subsequently reported in Palmer (2001). "Palmer2" gave only limited survival data.

We agree that this abstract teaches the claimed BLP25 dosage, but it doesn't overcome the deficiencies already noted above.

3. Definiteness

3.1. The examiner has questioned the parenthetical "(without pleural effusion)": is it an explanation of the meaning of "locoregional", or an optional further limitation? In the former case, it is superfluous. In the latter case, it is allegedly improper, since the claim then simultaneously has both a broader and a narrower scope.

Stage IIIB is defined in the specification at P26, L3-8. The term "IIIB locoregional" is used at P35, L5 and 13; P36, L28; P37, L7, 12, 17 and 19; tables 1 and 2; P41, L15. "IIIB locoregional" is contrasted with "IIIB with malignant pleural effusion" at P37, L12 and Tables 1 and 22. See also original claim 12. Hence, it appears that the best supported term is "IIIB locoregional", but that this should be understood to be without malignant pleural effusion.

It is possible that the absence of malignant pleural effusion is part of the definition of locoregional (as implied by placing it in parentheses), but to avoid doubt as to whether MPE is permissible, we have expressly excluded it by removing the parentheses, so "without malignant pleural effusion" is a further limitation in both claims 1 and 18.

3.2. The examiner says that claims 7-8 are incomplete because they do not recite how the patients are evaluated. Claim 7 has been amended to require evaluating at least the cancer state (cp. claim 11) or immunological activity (cp. claims 9-10) of the individual.

Claim 8 has been cancelled because it is not seen how in a practical sense it further limits claim 7 (the evaluating is said to be before, during, or after step (b), or a combination thereof). Thus, it is cancelled for reasons unrelated to the stated rejection.

4. Written Description

The examiner concedes enablement for SID 1 and 2 but not for the full breadth of the claim, which includes variants of those sequences. The examiner says that we have not taught where the sequences can and cannot be modified.

In view of this rejection, we have amended claims 1 and 18 to require that the polypeptide comprise "an amino acid sequence selected from the group consisting of

(1) amino acid sequences comprising at least five consecutive amino acids of any of SEQ ID NOs:1-8 and

(2) amino acid sequences which are at least 80% identical to any of SEQ ID NOs:1-8.

The examiner will appreciate that clauses (1) and (2) are based on claims 31 and 32 respectively.

It is well known in the art that MUC1 comprises a 20 aa core repeat sequence with desirable immunological properties. The exemplified SID1 and SID2 comprise 1¼ such repeats.

SID 3-8 are six of the 20 possible permutations of the 20 aa MUC-1 core repeat. Two subsequences are found in all of SID 1-8, these are STAPP and PDTRPAPG, and we respectfully submit that this contemplates "information about which amino acids can vary...."

Also, at page 12, lines 4-13, applicants teach

> A MUC-1 core repeat protein of the present invention may be modified to contain conservative variations or may be modified so as to change non-critical residues or residues in non-critical regions. Amino acids that are not critical can be identified by methods known in the art, such as site-directed mutagenesis, crystallization, nuclear magnetic resonance, photoaffinity labeling, or alanine-scanning mutagenesis (Cunningham *et al.*, *Science*, *244*:1081-1085 (1989); Smith *et al.*, *J. Mol. Biol.*, *224*:899-904 (1992); de Vos *et al.*, *Science*, *255*:306-312 (1992)). Modified proteins can be readily tested for activity or ability to induce an immune response via methods such as protease binding to substrate, cleavage, *in vitro* activity, or *in vivo* activity.

Conservative substitutions are defined at P12, L24-29, and a limitation to 1-5 substitutions is suggested by P12, L14. Percentage identities more stringent than 80% are disclosed at P12, L1-3. Moreover, there is an art recognized correlation between MUC1 core repeat fragments and immunological activity.

For example, as stated in Koganty, et al., PCT/US03/10750, filed April 9, 2003, entered US national stage as 10/511,101 and published domestically as US Patent Pub 20060069238 [docket Koganty4A-USA], at page 62,

> Von Mensdorff-Pouilly et al., Int. J. Cancer, 86:702-12 (Jun. 2000) reported that the most frequent minimal epitopic sequences of natural MUC1 IgG and IgM antibodies were RPAPGS (AAs 9-14 of SEQ

ID NO:10), PPAHGVT (AAs 4-10 of SEQ ID NO:11; equivalent to AAs 17-20 followed by AAs 1-3 of SEQ ID NO:10) and PDTRP (AAs 6-10 of SEQ ID NO:10). MUC1 peptide vaccination induced high titers of IgM and IgG antibodies predominantly directed, respectively, to the PDTRPAP (AAs 6-12 of SEQ ID NO:10) and the STAPPAHGV (AAs 1-9 of SEQ ID NO:2) sequences of the tandem repeat.

See generally pp. 58-66 of Koganty4A-USA.

The range of allowable polypeptides is further constrained by amended claims 31-32 and new claims 33-39 (all dependent on claim 1) . Hence, even if the examiner still believes that new claim 1 lacks written description, consideration should be given to whether claims 31-39 satisfy the written description requirement. We are willing, of course, to add claims like 31-39 but dependent on claim 18.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By: _____
Iver P. Cooper
Reg. No. 28,005

Enclosures
-press release 2009
-Kallen 2007 (pages 1, 10, 11)
-Sangha 2007
-Butts 2005

624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone: (202) 628-5197
Facsimile: (202) 737-3528
IPC:lms

G:\ipc\a-c\biom\Longenecker7a\longenecker7a.pto amend.wpd